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REVIEW ARTICLE

Thalidomide: Current Role in the Treatment of Non-Plasma Cell Malignancies

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A B S T R A C T

Thalidomide, initially introduced as a sedative, was withdrawn from the market in the early 1960s after it was found to be a teratogen. However, it later found use as an investigational agent in the treatment of erythema nodosum leprosum, oral ulcers, graft versus host disease, and wasting associated with the human immunodeficiency syndrome. Its antiangiogenic properties were recognized in the early 1990s during a period where the importance of angiogenesis became increasingly apparent as a critical step in the in the proliferation and spread of malignant neoplasms. This led to the evaluation of thalidomide as an antiangiogenic agent in the treatment of several cancers. Thalidomide has already become part of standard therapy for the treatment of patients with relapsed and refractory multiple myeloma. It has also been found to have varying degree of benefit in various other malignancies. Although more clinical trials are needed, Kaposi's sarcoma and myelofibrosis represent other malignancies in which thalidomide has already demonstrated promising activity. The mechanism of action of thalidomide in cancer is still unclear, but do appear to be mediated by several other mechanisms in addition to its anti-angiogenic properties. This article reviews the current status of thalidomide for the treatment of non–plasma-cell malignancies.

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Thalidomide was first marketed as a sedative in the 1950s and withdrawn from the market following reports of teratogenicity in 1961.[1,2] Since that time, new uses for the drug have emerged, including the treatment of erythema nodosum leprosum,[3] aphthous ulcers of Behcet's disease,[4] wasting and oral ulcers associated with the human immunodeficiency syndrome,[5,6] and graft versus host disease.[7] These indications allowed continued availability of thalidomide in a restricted manner, primarily through clinical trials and for compassionate use. In 1998, the United States Food and Drug Administration approved thalidomide for use in erythema nodosum leprosum. Access to thalidomide in the United States requires participation in the System for Thalidomide Education and Prescription Safety (STEPS) program to prevent teratogenicity.[8]

Recently numerous studies have shown that thalidomide has significant activity in the treatment of multiple myeloma.[9-11] In fact, myeloma has rapidly become the most common indication for the use of thalidomide in clinical practice. Recent reviews have summarized the role of thalidomide in myeloma and related plasma cell malignancies.[12,13] Besides myeloma, clinical trials have been conducted with the drug in several hematologic and nonhematologic malignancies as well. These trials have shed light on other promising aspects of thalidomide in the treatment of cancer. This review summarizes the available literature on the use of thalidomide in non–plasma-cell malignancies and the current role of thalidomide in these disorders.

Brief Historical Overview

Soon after its teratogenic properties were detected, oncologists were hopeful that the powerful inhibitory effect of thalidomide on growing fetal tissues can be redirected for cancer therapy.[14] This interest in studying thalidomide as an anticancer agent led to at least three trials in the early 1960s.[15,16] The Eastern Cooperative Oncol-

ogy Group studied 21 patients with 14 types of advanced cancer, including two with myeloma at doses ranging between 600 and 2,000 mg/d.[16] Subjective palliation of symptoms was noted in one-third of the patients. However, other than minimal slowing of tumor growth in two patients with rapidly progressive disease, no significant antitumor effects could be discerned. In another study, thalidomide was evaluated in 71 patients with a variety of cancers at doses ranging from 300 to 2,000 mg/d.[15] Except for resolution of pulmonary metastasis in a patient with renal cell carcinoma, no other responses were seen. There was at least one other negative study conducted during that time period. Following these initial unimpressive trials, there was little enthusiasm regarding thalidomide as an antineoplastic agent until the late 1990s.

The resurgence of interest in this drug as an antineoplastic agent in the last decade coincided with two key scientific observations. One was the heightened appreciation of the role of angiogenesis in cancer biology,[17,18] especially after the discovery of angiostatin and endostatin, two potent antiangiogenic compounds.[19,20] The other was the discovery that thalidomide possessed potent antiangiogenic properties.[21,22] Angiogenesis (sprouting of new microvasculature from existing blood vessels) is critical for the proliferation and metastases of most malignant neoplasms. In its absence, tumors cannot grow beyond 1 to 2 mm in size.[18] Based on the increased angiogenesis noted in myeloma, researchers at the University of Arkansas tested the role of thalidomide in 84 patients with relapsed and refractory myeloma.[9] They observed a 32% response rate, including two complete remissions (CRs), in this heavily pretreated population, making thalidomide the first new agent for myeloma in over three decades. Although clinical trials with the drug in several tumors were already ongoing, it was this dramatic effect in myeloma that ushered thalidomide as a legitimate anticancer agent for further research.

Pharmacology

Thalidomide (α-*N*-[phthalimido] glutarimide, $C_{13}H_{10}N_2O_4$), is a glutamic acid derivative and contains a glutarimide moiety with a single chiral center. It is formulated as a racemic mixture of the two optically active *S* (−) and *R* (+) enantiomers. These enantiomers can rapidly interconvert at physiologic pH and have different biologic effects—the *S* enantiomer being primarily responsible for the teratogenic effects, and the *R* enantiomer for the sedative properties.[23]

At present, thalidomide is only available as an oral formulation. Poor water solubility of this compound and the lack of an intravenous formulation have hampered reliable pharmacokinetic studies of this agent. However, healthy volunteer studies as well as studies in HIV patients and patients with prostate cancer have shown that the time to peak concentration varies from 3 to 6 hours, indicating a slow absorption.[24-26] Though there is reasonable correlation between the dose and the area under the curve, significant variability is seen in the maximum concentration, probably reflecting its poor absorption.[27] There is no significant drug binding by plasma proteins, and it has a large apparent volume of distribution as noted in human and animal studies.[25,26] It has been shown to be present in semen after a period of 4 weeks of therapy and levels appear to correlate with serum levels.[28]

The majority of the drug appears to undergo spontaneous nonenzymatic hydrolytic cleavage in the blood circulation into over 12 metabolites, many of which are metabolically active. Though in vitro studies in rats suggest a role for the cytochrome P450 system in its metabolism, human studies have so far failed to demonstrate any significant hepatic metabolism.[29,30] However, in an immunodeficient mouse myeloma model, thalidomide demonstrated efficacy only in the presence of implanted human liver tissue.[31] Differences have been noted in terms of the drug metabolism between mice and humans.[32]

Elimination of thalidomide is mainly by the spontaneous hydrolysis, which occurs in all body fluids, with an apparent mean clearance of 10 l/h for the (R)-enantiomer and 21 l/h for the (S)-enantiomer in adult subjects.[33] This leads to higher blood concentrations of the (R)-enantiomer compared to those of the (S)-enantiomer. The mean elimination half-life of both enantiomers is about 5 hours. The pharmacokinetics of thalidomide in individuals with hepatic and renal dysfunction remains poorly understood. No induction of its own metabolism has been noted with prolonged use.[34] Thalidomide and its metabolites are rapidly eliminated in the urine, with none of the parent compound detected in the urine 48 hours following a single dose.

Adverse Effects and Dose

Teratogenicity is the most feared adverse event, and occurs when taken between days 27 and 40 of gestation.[35,36] Fetal abnormalities include malformed and markedly shortened extremities (phocomelia) and deformities of the ears, eyes, and the gastrointestinal tract. In the United States, thalidomide (Thalomid, Celgene Corporation, Warren, NJ) is marketed under STEPS program to prevent teratogenic complications. Under this program, women in the childbearing age group must undergo pregnancy testing before starting therapy, and every 2 to 4 weeks during treatment. They must abstain from sexual intercourse, or use two highly effective contraceptive methods, during treatment. Males must abstain from sexual intercourse or use a condom while on treatment even if they have had a successful vasectomy. All patients must continue the above measures for at least 1 month following the last dose of the drug. Breastfeeding is contraindicated while on the drug.

In addition to its teratogenic potential, thalidomide therapy is associated with many other potential side effects (Table

Table 1. Adverse Effects of Thalidomide Therapy

Frequent Side Effects	Less Common Side Effects
Birth defects	Headache
Drowsiness and somnolence	Confusion
Skin rash	Malaise
Constipation	Asthenia
Peripheral neuropathy	Hyper- or hypoglycemia
Xerostomia	Tremor
Orthostatic hypotension and dizziness	Pruritus
Neutropenia	Peripheral edema
	Hepatitis (elevated serum transaminases)
	Stevens-Johnson syndrome
	Impotence
	Deep vein thrombosis
	Hair loss
	Loss of libido
	Nausea
	Fever
	Menstrual abnormalities
	Hypothyroidism

1). The frequency, management, and prevention of these adverse events has been recently reviewed.[37] In general, at doses below 400 mg/d, thalidomide is well tolerated. Most side effects are mild or moderate in severity (Table 1), and can be controlled by appropriate dose reduction. Sedation, fatigue, skin rash, and constipation are among the most commonly encountered side effects. Since severe constipation is a common problem, prophylactic laxatives are recommended routinely. Minor to moderate skin eruptions were noted in nearly half of patients taking thalidomide alone or with dexamethasone in one review.[38] These included morbilliform, seborrheic, maculopapular, or nonspecific dermatitis. Thalidomide should be discontinued if symptomatic skin rash appears, and restarted at a lower dose after it clears. Rarely, severe dermatologic reactions like Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis occur and preclude any further use of the drug.[39] Longer-term use of thalidomide (usually over 6 months) can cause peripheral neuropathy. Less common side effects include bradycardia, impotence neutropenia, menstrual irregularities, edema, increased liver enzymes, deep vein thrombosis, hyper- or hypoglycemia, and hypothyroidism. Thromboembolic events appear to be higher when used along with other chemotherapy agents or dexamethasone.[40-43] Hyperkalemia has been reported in patients with myeloma and renal failure.[44]

The optimal dosing schedule for thalidomide as an antineoplastic agent is not known. Most of the clinical trials in cancer have used doses between 200 and 800 mg/d, taken orally as a single dose at bedtime. The usual starting dose in myeloma trials has been 200 mg/d, increased by 200 mg every 2 weeks to a maximum of 800 mg/d, final dose determined by the toxicity profile. The optimal dose for each patient is probably the highest dose that patients can tolerate with the minimum of side effects, which in most patients is between 200 and 400 mg/d. It is not clear if a definite dose response relationship exists, or whether smaller doses of can be equally effective with lesser side effects. At least in the setting of myeloma, some studies have suggested the possibility of a dose-response effect.[45]

Mechanism of Action

Clues to the mechanism of action of thalidomide in cancer probably lie in its potent teratogenic ability, but have been difficult to unravel due to several reasons. First, mechanistic studies with thalidomide are complicated by its enantiomeric inter-conversion and spontaneous cleavage to many metabolites.[33] Second, thalidomide probably requires some form of metabolic activation, since in vitro assays show modest or negligible activity, compared to highly potent effects in vivo.[30,46] Third, no specific receptor has been identified for any of the drug's myriad of clinical effects, including toxicities such as sedation and constipation. Finally, various effects in animal models appear to be highly dependent on species and route of administration, making correlations to humans complicated and unreliable.[22]

Many mechanisms have been put forth to explain the antineoplastic activity of thalidomide; and myeloma has been particularly well studied (Fig 1). Although the direct in vitro effects of thalidomide on tumor cells are unimpressive, it is felt that thalidomide targets both the cancer cell and its microenvironment. D'Amato et al[21] and Kenyon et al[22] showed that thalidomide is a potent antiangiogenic agent using in vivo models of angiogenesis. Animal studies support this hypothesis since thalidomide treatment can decrease vascular density in granulation tissue.[47] Studies suggest that a hepatic metabolite of thalidomide may be responsible for its antiangiogenic effects.[46] Despite its known antiangiogenic properties, there has been some debate about whether this is involved in the antitumor effects of thalidomide.

Based on the studies done in the context of erythema nodosum leprosum, thalidomide has been shown to have an anti-tumor necrosis factor-alpha (TNF-α) action.[48] Thalidomide inhibits the production of TNF-α by enhancing the degradation of TNF-α mRNA.[48] It may also bind to and increase the effect of α1-acid glycoproteins, which possess intrinsic anti-TNF-α activity.[49,50] In the setting of myeloma, anti-TNF-α activity may play a role. High pretreatment TNF-α levels appear to predict progression-free survival after thalidomide in patients with myeloma.[51] In addition, DNA polymorphisms involving the TNF-α gene have been correlated with response to thalidomide in myeloma.[52]

The antitumor properties are also probably related to its immunomodulatory effects and effects of cellular adhesion molecules. Thalidomide has direct effects on the T-lymphocytes stimulating cytotoxic T-cell proliferation,

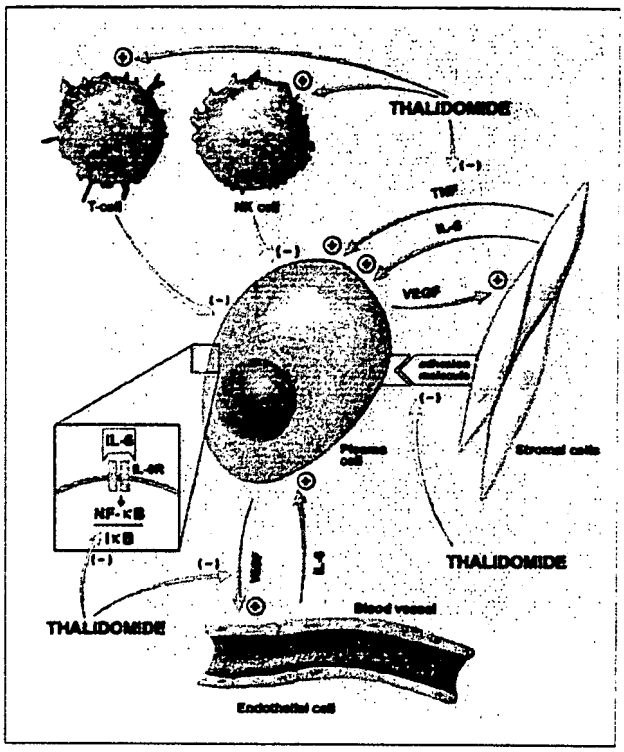

Fig 1. Proposed mechanism of action of thalidomide in cancer illustrated using myeloma as an example. Thalidomide inhibits angiogenesis, enhances effects of the immune system, inhibits binding of tumor cells to stroma, and inhibits various cytokines. Thalidomide may also have direct effects on the tumor. NK, natural killer; TNF, tumor necrosis factor; IL-6, interleukin-6; VEGF, vascular endothelial growth factor; NF-κB, nuclear factor kappa B.

and induction of secretion of interferon-γ and interleukin-2 (IL-2).[53] In healthy male volunteers given 200 mg/d for 4 days, it significantly decreased the circulating T-helper to T-suppressor cell ratio.[54] It also induces T-helper cell type 2 cytokine production in human peripheral blood mononuclear cell cultures, while concomitantly inhibiting T helper cell type 1 cytokine production.[55] Some of its antitumor activity of thalidomide and its derivatives may be mediated by modulation of natural-killer cell activity.[56] Thalidomide can modulate the expression of cell surface adhesion molecules like TNF-α, intercellular adhesion molecule-1 (CD54), vascular cellular adhesion molecule-1 (CD106), E-selectin and L-selectin (CD62L).[57] Other suggested mechanisms for antitumor effects include inhibition of nuclear factor-kappa B activity through suppression of I-kappa B kinase activity and inhibition of the cyclooxygenase 1 and 2 enzymes.[58,59]

The mechanism of action of thalidomide including effects on tumor microenvironment, vascular endothelial growth factor (VEGF), plasma cell apoptosis, and angiogenesis are all being actively investigated.[49] Although it is tempting to believe that the drug has several effects at various stages of tumor growth and dissemination, we think that it is more likely that a single as yet unidentified target is involved, given that the mechanisms discussed above are in general important in almost all cancers, while responses seen with this agent occur in very selected tumor types.

Solid Tumors

Thalidomide has been investigated in several solid tumors with variable degrees of success. Table 2 summarizes the results of published clinical trials with thalidomide in solid tumors.

Malignant Melanoma

Thalidomide used alone in a low dose did not produce any response among patients with metastatic melanoma.[64] Even at higher doses, thalidomide when used alone has led to disappointing results.[78] Thus, most of the recent studies have used thalidomide in combination with other active agents such as dacarbazine or temozolomide (TMZ) in the treatment of metastatic disease. Hwu et al[79] studied thalidomide in combination with temozolomide in patients with unresectable stage III or stage IV melanoma without brain metastases. TMZ (75 mg/m2/d) for 6 weeks was followed by a 2-week break, and thalidomide at 200 to 400 mg/d. Thirty-eight patients were treated, and 10 patients (26%) showed partial response (PR); four other patients showed minor response and three had a mixed response. The most common side effects included rash, constipation, vomiting, dizziness, dyspnea, fatigue, headache, drowsiness, hyperglycemia, and elevation of liver enzymes.

A randomized phase II study compared TMZ alone, TMZ combined with interferon alfa-2b and TMZ combined with thalidomide.[77] One hundred eighty-one patients with metastatic melanoma were randomly assigned to one of the three regimens. Response or disease stabilization occurred in 25% of the patients treated with TMZ plus thalidomide combination, 20% receiving TMZ alone and 21% of those given TMZ plus interferon. Median survival was 7 months for the TMZ/thalidomide arm, 5 months for the TMZ alone arm, and 8 months for the TMZ plus interferon (not significantly different across the three groups).

At present, the role of thalidomide in melanoma is investigational and its use should be restricted to clinical trials. Again, given the disappointing results when used alone, thalidomide should be studied further in combination with chemotherapeutic agents with known activity in this disease. Results of ongoing and future clinical trials will further define its role.

Renal Cell Cancer

Thalidomide has shown promising activity in renal cell carcinoma (RCC) in several clinical trials. Stebbing et al[67] evaluated the use of high-dose oral thalidomide (600 mg daily) in 25 patients with advanced renal carcinoma, who had either progressed on or were not suitable for immunotherapy. Of the 22 assessable patients, two showed PRs

Table 2. Clinical Trials of Thalidomide Alone or in Combination for Solid Tumors

Disease	Trial Type	No. of Patients	Regimen	Thal Dose (mg/day)	Efficacy (CR or PR)	Side Effects
Prostate cancer						
Figg et al[60]	Phase II randomized	63	Thal	200-1,200	27%	Fatigue, hypergiycemia, pulmonary toxicity, thrombotic events
Drake et al[61]	Phase II	20	Thal	100	15%	Constipation, morning drowsiness, dizziness, neuropathy, rash
Figg et al[62]	Phase II	36	Thal + docetaxel	200	53%	Constipation, dizziness, edema, fatigue, mood changes, peripheral neuropathy
Breast cancer						
Baidas et al[63]	Phase II	28	Thal	200-800 or 1,200	No true PR or CR	Constipation, somnolence, fatigue, peripheral neuropathy, dizziness and instability, dry mouth, skin rash, nausea
Eisen et al[64]	Phase II	12	Thal	100	NR	Lethargy, neuropathy
Kaposi's sarcoma						
Fife et al[65]	Phase II	17	Thal	100	35%	
Little et al[66]	Phase II	20	Thal	200-1,000	47%	Neuropathy, depression, somnolence, fatigue
Renal cell cancer						
Stebbing et al[67]	Phase II	25	Thal	600	9%	Lethargy, constipation, neuropathy
Motzer et al[68]	Phase II	26	Thal	200-800	62% (SD only)	Dyspnea, neuropathy, thrombosis, fatigue, rash
Daliani et al[69]	Pilot	20	Thal	200-1,200	10%	Constipation, somnolence, fatigue, peripheral neuropathy
Escudier et al[70]	Phase II	40	Thal	400-1,200	5%	Fatigue, constipation, lethargy, neuropathy, thromboembolism
Minor et al[71]	Phase II	29	Thal	400-1,200	5%	Somnolence, constipation
Brain						
Fine et al[72]	Phase II	36	Thal	800-1,200	12% (33% SD)	Constipation, sedation, neuropathy
Short et al[73]	Phase II	18	Thal	100	6%	Neuropathy
Marx et al[74]	Phase II	42	Thal	100-500	5% (42% SD)	Fatigue
Fine et al[75]	Phase II	40	Thal + BCNU	800-1,200	24%	Sedation, myelosuppression
Melanoma						
Hwu et al[76]	Phase II	38	Thal + Temozolomide	100-250	10%	Rash, constipation, vomiting, dizziness, dyspnea, fatigue, headache, drowsiness, hyperglycemia, liver enzyme elevation
Danson et al[77]	Phase II	60 (Thal arm)	TMZ *v* thal/TMZ *v* IFN/TMZ	100	25%	Constipation, lethargy

Abbreviations: Thal, thalidomide; CR, complete response; PR, partial response; NR, no response; SD, stable disease; BCNU, carmustine; TMZ, temozolamide; IFN,interferon.

(9%), seven (32%) had stable disease for more than 6 months, and five (23%) other patients had stable disease for between 3 and 6 months. In patients with stable disease for 3 or more months or objective response, a significant decrease in serum TNF-α levels was seen.

Several recent studies have looked at escalating doses of thalidomide to as high as 1,200 mg/d (Table 2). In one phase II trial, 40 patients with metastatic renal cell cancer (RCC) were treated at a starting dose of 400 mg, followed by a 400 mg increment to 800 mg and then to 1,200 mg with 6 to 12 weeks at each dose level.[70] Two PRs were observed (5%) and disease remained stable in nine patients after 6 months. Median survival was 10 months. There was significant toxicity, mainly fatigue, constipation, lethargy, neuropathy,

and venous thromboembolism. In another study, 20 patients with metastatic RCC were treated at doses starting at 200 mg escalating to 1,200 mg/d.[69] Two patients achieved a PR, and nine had stable disease for a median of 14 months. The most common, but reversible toxicities were constipation, somnolence, and fatigue. Median time to progression was 4.7 months. Minor et al[71] studied 29 patients with metastatic RCC using escalating doses of thalidomide (400 mg/d and increased as tolerated to 1,200 mg/d). Among the 24 patients assessable for response, one had PR, one had minor response, and two patients had stable disease for over 6 months. Similar side effects were seen and doses over 800 mg/d were difficult to achieve in this trial.

Two studies have used lower doses of thalidomide. Motzer et al[68] treated 26 patients with advanced RCC with thalidomide at doses between 200 and 800 mg/d. Fifteen had prior nephrectomy, 11 had no prior systemic therapy, and 15 had received one prior systemic regimen. Of 25 assessable patients, the best response was stable disease in 16 patients. Progression-free survival at 6 months was 32%; 57% were alive at 1 year. Eisen et al[64] treated 18 patients with low-dose thalidomide (100 mg/d) and observed three PRs among 18 treated patients. An additional three patients had stabilization of their disease, and most patients tolerated therapy well.

Combination trials with thalidomide and other active agents are ongoing. Serious adverse events have been reported with the combination of interferon and thalidomide, including seizures and visual disturbances.[80] A randomized trial conducted by the Eastern Cooperative Oncology Group comparing interferon plus thalidomide versus interferon alone has recently met accrual and results are awaited. Thalidomide has been tested in combination with IL-2 and the combination appears to have activity with acceptable toxicity.[81] Amato et al[82] used thalidomide (400 mg daily) with interleukin-2 (7 mIU/m^2 subcutaneous days 1 to 5 on weeks 1 to 4, repeated every 6 weeks) in 37 patients. Of 36 assessable patients, there was one complete response and 14 PRs for a response rate of 42%. A recently initiated multicenter, randomized, double-blind study is comparing the efficacy and safety of thalidomide plus low-dose IL-2 versus low-dose IL-2 alone versus thalidomide alone in subjects with previously untreated metastatic renal cell cancer.

In summary, thalidomide as a single-agent has shown limited activity in RCC. Activity in combination with IL-2 is promising, but results of the ongoing randomized trial are needed. Thalidomide may be of benefit in combination with other active, synergistic agents, and this option needs to be explored in future clinical trials.

Kaposi's Sarcoma

The observation of Kaposi's sarcoma (KS) lesions improving in some individuals who were receiving thalidomide therapy for HIV-related oral ulcers, combined with the highly vascular nature of this tumor, formed the rationale for evaluating thalidomide in the treatment of KS. In a phase II study, 17 male HIV-seropositive patients with histopathologically diagnosed KS were treated with thalidomide 100 mg orally once nightly for 8 weeks.[65] Six of 17 patients achieved a PR associated with reduction in HHV-8 DNA load to undetectable levels in three of the responders. Thalidomide has also shown benefit in non–HIV-related KS.[83] Little et al[66] evaluated thalidomide in a phase II study with doses ranging from 200 to 1,000 mg/d given up to a year along with antiretroviral therapy. Eight of the 17 assessable patients achieved a PR, and an additional two patients had stable disease. Since most patients also received concurrent antiretroviral therapy in this trial, the investigators recommend caution in interpreting results. Additional studies are needed to define the role of thalidomide in KS.

Brain Tumors

Thalidomide was evaluated in patients with anaplastic mixed glioma, anaplastic astrocytoma, or glioblastoma multiforme who had tumor progression after radiotherapy with or without chemotherapy in a phase II trial.[72] Patients were treated with escalating doses of thalidomide starting at 800 mg/d, with increases in dose by 200 mg/d every 2 weeks to a final daily dose of 1,200 mg. Among 39 patients, there were two objective radiographic PRs (6%), two minor responses (6%), and 12 patients with stable disease (33%). Eight patients were alive more than 1 year after starting thalidomide, although almost all had tumor progression.

In another phase II trial, 18 patients with recurrent high grade gliomas were treated with 100 mg a day of thalidomide.[73] All patients had failed radiotherapy and chemotherapy with procarbazine, lomustine, and vincristine and/or temozolomide regimens. Six patients died before response could be fully assessed, and were classified as nonresponders. Of the 12 patients treated for more than 4 weeks, only one patient had clinical and radiologic response (PR); two patients had stable disease for 2 and 4 months, respectively. The median survival from the start of thalidomide was 2.5 months. Though the efficacy was low in this study, the authors felt that thalidomide should be further investigated in combination with other agents and at an earlier stage of disease.

Marx et al[74] published the results of a phase II trial in recurrent glioblastoma multiforme. Forty-two patients were treated with 100 mg/d, increased at weekly intervals by 100 mg to a maximum-tolerated dose of 500 mg/d (median maximum-tolerated dose was 300 mg/d). Of the 38 assessable patients, two patients (5%) achieved a PR and 16 (42%) had stable disease. The median survival was 31 weeks and the 1-year survival was 35%. Responding patients had some stabilization or improvement in quality of life scores or performance status. Overall, the drug

was well tolerated with no grade 4 toxicities and no treatment related deaths.

Glass et al[84] combined thalidomide with carboplatin for recurrent glioma. Thalidomide up to a dose of 300 mg/d was given continuously along with six cycles of carboplatin. Sixty-four patients were enrolled and 46 were assessable. Five patients (11%) had a PR and 28 had stable disease. The estimated median survival was 40 weeks and the median response duration was 24 weeks. Fine et al[75] used the combination of thalidomide and carmustine in patients with recurrent high-grade gliomas. Patients with high-grade glioma and radiographic evidence of tumor progression after standard surgery, radiation, and chemotherapy were treated with carmustine 200 mg/m^2 on day 1 every 6 weeks, and thalidomide was started at 800 mg/d and increased to a maximal dose of 1,200 mg/d as tolerated. Of 40 patients treated, 24% had an objective radiographic response. The combination was well tolerated, with mild myelosuppression and mild to moderate sedation being the most common side effects.

These results show that thalidomide as a single agent has only marginal activity in high-grade gliomas, with PR rates that are less than 10%. Give the inherent problems in assessing response in this patient population and minimal effects on survival, the use of thalidomide for high-grade gliomas should probably be considered only in the context of clinical trials. Also, given the disappointing single-agent activity, combinations with other active agents should be explored for synergistic activity.

Prostate Cancer

Thalidomide was studied in a phase II study evaluating two dosing regimens of thalidomide (200 mg/d *v* 1,200 mg/d) in androgen-independent prostate cancer. Sixty-three patients refractory to combined androgen deprivation were studied; 50 received 200 mg/d of thalidomide and 13 patients received 1,200 mg/d of thaldiomide.[60] A 50% or greater decrease in prostate-specific antigen (PSA) was noted in 18% of patients on the low-dose arm; no patients in the high-dose arm responded.

In another study, 20 patients with androgen-independent prostate cancer were treated with thalidomide 100 mg once daily. Three patients (15%) showed a decline in serum PSA of at least 50%.[61] Progressive disease was associated with increase in the levels of serum basic fibroblast growth factor (bFGF) and VEGF while responding patients had decline in levels of these angiogenic cytokines. Adverse effects included constipation, drowsiness, dizziness, and skin rash. Preclinical studies have suggested that thalidomide may increase the secretion of PSA from tumor cells and confound efficacy evaluation.[85]

Thalidomide was also studied in combination with docetaxel in a randomized phase II study in patients with androgen independent prostate cancer.[62] Thirty-five percent of the patients (six of 17) receiving docetaxel alone and 53% (19 of 36) of those receiving docetaxel and thalidomide had a PSA decrease of at least 50%. There was an increased rate of thrombotic events in the combination arm.

These studies show that thalidomide decreases PSA levels in 15% to 20% of patients with hormone refractory prostate cancer. However, more studies are needed to determine the usefulness of this agent in routine clinical practice in this setting, given that the response rate is small and other meaningful assessments of tumor burden need to be done.

Breast Cancer

Tumor angiogenesis has prognostic value in invasive breast cancer and it has been correlated with its metastatic potential.[86] In a phase II randomized study, Baidas et al[63] treated 28 patients with progressive metastatic breast cancer either daily 200 mg of thalidomide or 800 mg to be escalated to 1,200 mg. No patient had a true PR or complete response in this study at either of the dose levels. Toxicities including somnolence and neuropathy required dose reductions, especially in the higher dose arm. Others have also noted a lack of significant efficacy of low or higher doses of thalidomide in the treatment of breast cancer.[64] Thalidomide, at least when used alone, is ineffective in breast cancer. It is unclear if it will have any role as part of combination regimens.

Other Solid Tumors

Thalidomide has been studied in combination with irinotecan in metastatic colorectal cancer with some responses. Interestingly, thalidomide ameliorated the common side effect of irinotecan, namely diarrhea, enabling a larger number of patients to complete planned therapy.[87] Responses have been observed in patients with unresectable hepatocellular carcinoma, with thalidomide alone or in combination with Cox-2 inhibitors, capecitabine, or other agents. Phase II studies with thalidomide have also been conducted in malignant mesothelioma, small-cell lung cancer, and metastatic neuroendocrine tumors. In addition, case reports and pilot studies have documented isolated responses with thalidomide in other solid tumors, such as ovarian cancer.[88] Results so far do not support off-study use of thalidomide in any of these malignancies.

Thalidomide may also have a role in the palliative setting. Improved appetite, weight gain, and improvement in quality-of-life scores have been seen with thalidomide therapy in patients with advanced malignancies.[89] However, we do not feel that therapy with this agent for this purpose can be recommended at this time.

Hematologic Malignancies

The focus of this review is on non–plasma-cell malignancies, and so a detailed review of the current status of thalidomide in myeloma and related disorders is beyond the scope of this article. Briefly, several trials confirm that thalidomide as a single-agent produces response rates in approximately 25% to 35% of patients with relapsed refrac-

Table 3. Clinical Trials in Hematologic Malignancies Other Than Myeloma

Disease (regimen)	Trial Type	Assessable Patients	Thalidomide Starting Dose (mg/day)	Thalidomide Maximum Dose (mg/day)	Efficacy (CR or PR)	Major Side Effects
Waldenstrom's macroglobulinemia (thalidomide)[103]	Phase II	20	200	600	20%	Constipation, somnolence, fatigue, mood changes, peripheral neuropathy, skin rash
Waldenstrom's macroglobulinemia (BLT-D)[103]	Phase II	12	200	200	33%	Constipation, somnolence, fatigue, mood changes, peripheral neuropathy, skin rash
Waldenstrom's macroglobulinemia (BLT-D)[104]	Phase II	12	200	200	83%	Constipation, peripheral neuropathy, thrombosis
Primary systemic amyloidosis[105]	Phase I/II	16	200	600	25% (hematologic response)	Fatigue, neuropathy, constipation
Acute myelogenous leukemia[106]	Phase I/II	20	200	400	20%	Fatigue, constipation, rash, neuropathy
Myelodysplastic syndrome[107]	Phase I/II	83	200	400	31%	Fatigue, constipation, dyspnea, fluid retention, dizziness, rash, neuropathy, fever, headache
Myelodysplastic syndrome[108]	Phase I/II	30	100	400	30%	Constipation, fatigue, dizziness, dyspnea, neuropathy
Myelodysplastic syndrome[109]	Phase II	34	100	400	27%	Fatigue, rash
Non-Hodgkin's lymphoma[110]	Phase II	12	200	800	8% CR, 25% SD	Fatigue, peripheral neuropathy
Myelofibrosis with myeloid metaplasia[111]	Phase II	15	200	400	80% (platelet count improved)	Fatigue, constipation, thrombocytosis, neuropathy, rash sedation.
Myelofibrosis with myeloid metaplasia[112]	Pilot	12	100	600	60%	Constipation, fatigue, somnolence, neuropathy
Myelofibrosis with myeloid metaplasia[113]	Phase II	13	100	400	43% (improved anemia)	Somnolence, fatigue, constipation

Abbreviations: CR, complete response; PR, partial response; BLT-D, clarithromycin, thalidomide, and dexamethasone; SD, stable disease.

tory myeloma.[9,13] The median duration of response is 1 year.[90,91] Response rates in relapsed disease increase to approximately 50% with the addition of corticosteroids,[92] and to over 65% with the addition of corticosteroids and cyclophosphamide.[93] Several other combination chemotherapy regimens containing thalidomide are being studied including dexamethasone, thalidomide, cisplatin, adriamycin, cyclophosphamide and etoposide,[94] clarithromycin 500 mg twice daily, low-dose thalidomide 50 mg/d, and dexamethasone,[95] melphalan, thalidomide, and dexamethasone,[96] and melphalan plus thalidomide.[97] In newly diagnosed myeloma, the combination of thalidomide plus dexamethasone has responses in the range of 65% to 70%.[98,99] Thalidomide alone or in combination is also being studied in early stage myeloma,[100] as maintenance therapy for patients who have undergone autologous stem-cell transplantation[101] and as consolidation therapy following autologous stem-cell transplantion in an attempt to convert partial remission to CR.[102]

In Waldenström's macroglobulinemia, thalidomide as a single-agent had a response rate of 25% in a small phase II clinical trial[103] (Table 3). The combination of clarithromycin (500 mg bid), low-dose thalidomide (200 mg once daily), and dexamethasone (40 mg once per week) has also been studied in two trials,[104] and demonstrated activity in this disease. Activity in primary amyloidosis is being investigated,[105] but preliminary reports suggest higher rate of adverse events in this group.

The encouraging results seen with other plasma cell proliferative disorders have led to the initiation of clinical trials evaluating the role of thalidomide in primary systemic amyloidosis. Seldin et al[114] presented the results of a phase I/II trial of thalidomide as a single agent in twelve patients with amyloidosis. Five of eleven patients had hematologic improvement. Three patients had stable disease and three had progressive disease. However, in this trial as well as in other studies, significant toxicities were observed with the use of thalidomide, especially at higher doses.

Based on current data, thalidomide is a standard treatment option for patients with relapsed myeloma, alone or in combination with corticosteroids. It can be considered for patients with Waldenström's macroglobulinemia who are refractory to other standard regimens. Its role in combination with other active chemotherapeutic agents, as initial therapy and as maintenance, following transplantation in myeloma and in the therapy of primary systemic amyloidosis is investigational.

Myelofibrosis With Myeloid Metaplasia

Increased bone marrow angiogenesis has been demonstrated in patients with myelofibrosis/myeloid metaplasia (MMM), leading to the evaluation of thalidomide in this condition (Table 3).[115] In a prospective study of 15 patients with MMM conducted at the Mayo Clinic (Rochester, MN), treatment with thalidomide resulted in increased

platelet counts (12 of 15 patients), increased hemoglobin level (three of 15 patients), modest decrease in spleen size (three of 12 patients), increased bone marrow megakaryopoiesis (five of nine patients), and decreased bone marrow angiogenesis (two of nine patients).[111] Although improvements in cytopenias were seen in this trial at conventional doses of thalidomide (200 to 400 mg/d), serious myeloproliferative reactions, including marked leucocytosis and thrombocytosis were observed in a few patients.[116] In another study of 13 assessable patients who received more than 30 days of therapy (100-400 mg/d), Barosi et al[113] noted improvement in anemia in three (43%) of seven patients, improvement in thrombocytopenia in two (67%) of three patients, and reduction in splenomegaly in four patients (31%). Serious myeloproliferative reactions were noted in this study as well. These initial studies concluded that lower doses of the drug need to be tested to minimize toxicity. There was a suggestion in the Mayo Clinic study that there was no loss of efficacy in patients in whom the dose was reduced to as low as 50 mg/d.

Reduction in bone marrow angiogenesis have been noted in patients treated with thalidomide along with reduction in the angiogenic cytokines VEGF and fibroblast growth factor in responding patients.[112] There has been one negative study, in which significant side effects were seen with no beneficial responses.[117] In a pooled-analysis of the data from five phase II trials including 62 patients, a small but clear improvement of disease severity with thalidomide therapy was noted.[118] Twenty-nine percent of patients with moderate to severe anemia showed an increase in hemoglobin or reduction/abolishment of blood transfusion requirements, 38% with moderate to severe thrombocytopenia had an increase in platelet counts, and 41% demonstrated a reduction in splenomegaly. Nearly 18% of the patients had a myeloproliferative reaction with leukocytosis and/or thrombocytosis. Sixty-six percent of the patients discontinued the drug before 6 months of treatment as a result of intolerance.

Based on the promising results with single-agent therapy, the combination of thalidomide with corticosteroids was evaluated in 21 symptomatic patients (hemoglobin level < 10 g/dL or symptomatic splenomegaly).[119] Patients received low-dose thalidomide (50 mg/d) to minimize serious myeloproliferative reactions along with a 3-month oral prednisone taper (beginning at 0.5 mg/kg/d). The combination was well tolerated, with all but one patient completing 3 months of treatment. An objective clinical response in the form of improvement in anemia was seen in 13 (62%) patients. Improvement in platelet count was seen in four of eight patients with thrombocytopenia. In four of 21 patients (19%), spleen size decreased by more than 50%. Responses observed were durable after discontinuation of corticosteroids in most of the patients.

In summary, low-dose thalidomide (50 mg/d) with prednisone is a reasonable therapeutic choice for patients with MMM who have cytopenias as the dominant manifestation of their disease. Further studies are needed for MMM patients with marked splenomegaly.

Myelodysplastic Syndrome

Several studies have been conducted examining the activity of thalidomide in myelodysplastic syndrome (MDS) and initial results are promising (Table 3). In a small study evaluating the effect of thalidomide in hematologic conditions associated with increased angiogenesis, Bertolini et al[120] noted clinical responses in two of the five patients with MDS they studied. They also noted a simultaneous decrease in the angiogenic cytokines bFGF and VEGF with response in these patients. Raza et al[107] studied 83 patients with MDS and noted hematologic improvement among 31% of assessable patients including transfusion independence in nine patients who were previously transfusion dependant. In another study, 30 patients with MDS were treated with 100 to 400 mg/d of thalidomide resulting in hematologic improvement in a third of the patients.[108] They studied the levels of apoptosis, macrophage number, microvessel density, TNF-α, transforming growth factor beta (TGF-β), IL-6, VEGF, and bFGF in the serum, bone marrow (BM) plasma and BM biopsies before and after therapy, and found a decrease in only BM TGF-β. In the latter two studies, patients with higher platelet counts and lower blast percentage at initiation of therapy were likely to respond. Finally, Strupp et al[109] studied 34 patients with MDS; five T-refractory anemia with excess blasts in transformation (RAEB-T), four refractory anemia with excess blasts, three chronic myelo-monocytic leukemia, six refractory anemia with ringed sideroblasts, and 16 refractory anemia with 400 mg/d of thalidomide. Nineteen of 29 assessable patients had hematologic improvement; six patients (four refractory anemia, two chronic myelomonocytic leukemia) showed progressive disease, and four patients showed stable disease. Nine of the responders achieved partial remission with granulocytes $\geq$ 1,500/microl, Hb $>$ 11 g/dL, and platelets $\geq$ 100,000/microl; four patients became transfusion independent.[109] Strupp et al[121] have also recently shown normalization of counts with cytogenetic responses in three patients with MDS following therapy with thalidomide. Combination of darbopoietin with thalidomide in patients with MDS was associated with increased thromboembolic events in a small study.[122]

Although thalidomide therapy is associated with improvements in cytopenias in patients with MDS, more data are still needed on effects of the drug on the clonal tumor cell population, cytogenetic responses, and progression of MDS to acute myeloid leukemia (AML). A randomized trial is currently ongoing to determine the role of thalidomide in MDS. Based on the available data it would be reasonable

to initiate a therapeutic trial of thalidomide in patients with refractory cytopenias secondary to MDS who are not candidates for ongoing clinical trials. The new thalidomide analog (CC-5013) may have a better therapeutic effect in this disease compared to thalidomide.

Acute Myelogenous Leukemia

In vitro studies on leukemia cell lines have demonstrated retinoid-like activity for thalidomide leading to differentiation of K562 leukemia cell line, as well as cytotoxic effect by the thalidomide metabolites.[123] This, in addition to the demonstration of increased bone marrow angiogenesis in patients with acute leukemias,[124] have led to the evaluation of thalidomide for the treatment of acute leukemias. Steins et al,[106] in a phase I/II dose-escalating trial, studied the efficacy of thalidomide in 20 patients with AML. Thirteen patients who completed the trial received doses of 200 to 400 mg daily for at least 1 month. Adverse events were similar to those in other studies. Four patients had a reduction of at least 50% in the blast cell infiltration of the bone marrow with improvement in peripheral blood counts. The responses lasted a median of 3 months (range, 1 to 8 months). They observed a significant decrease in the microvessel densities in the responding patients treated with thalidomide, which was accompanied by declining plasma levels of bFGF.

At this time, despite preliminary results from Steins et al,[122] there are limited data to support the use of thalidomide in AML outside of clinical trials.

Non-Hodgkin's Lymphoma

The role of angiogenesis is increasingly recognized in the pathogenesis of lymphoid malignancies.[125] Elevated serum levels of VEGF and bFGF have been correlated with poor prognosis in patients with non-Hodgkin's lymphoma (NHL).[126] Preliminary results are available from a phase II study of thalidomide in patients with recurrent NHL and Hodgkin's disease without CNS involvement, 18 patients received thalidomide at a starting dose of 200 mg daily.[110] The dose was escalated by 200 mg every 2 weeks until a maximum of 800 mg based on toxicity and tolerability. Median age was 66 years (range, 30 to 78 years) and the median number of prior treatments was five (range, 3 to 7 treatments). The diagnoses included small lymphocytic lymphoma (three patients), follicular small cleaved (three patients), large B-cell lymphoma (six patients), mantle-cell lymphoma (two patients), Hodgkin's disease (two patients), and one each of mucosa-associated lymphoid tumors (MALT) and peripheral T-cell lymphoma. A maximum dose of 800 mg, 600 mg, 400 mg, and 200 mg was reached in seven (41%), five (29%), two (11%), and three (17%) patients respectively, and one patient is still on escalating doses. Of 12 assessable patients, one patient achieved CR (refractory MALT lymphoma of the stomach) and three patients had stable disease. Grade 2/3 neurologic toxicity was observed in six patients; grade 2/3 fatigue occurred in 16 patients. Reductions of plasma levels of VEGF and bFGF were observed in the one patient who achieved CR. No significant decreases in plasma levels of angiogenic factors were observed in patients with stable disease.

Thalidomide has recently been reported to be effective in the treatment of angioimmunoblastic lymphadenopathy.[127] There have been case reports of patients with mantle-cell lymphoma responding to thalidomide.[128]

We feel that thalidomide has not shown significant activity in NHL and available data are too premature to make definite conclusions. However, clinical trials in MALT and mantle-cell lymphoma may be of interest.

Future Directions

In clinical trials with thalidomide so far, responses as dramatic as those observed in multiple myeloma have not been observed in other hematologic malignancies and solid tumors. Nevertheless, thalidomide has shown promising activity in two hematologic malignancies, namely MMM and MDS. In MMM, the addition of prednisone to low-dose thalidomide appears to prevent serious myeloproliferative reactions and improve efficacy. Trials in solid tumors again have demonstrated useful activity for this drug, especially in Kaposi's sarcoma and malignant melanoma. The efficacy of adding thalidomide to other effective drug combinations continues to be explored in various malignancies.

Compared to myeloma, the amount of data is still limited in almost all other malignancies in which thalidomide has shown promising activity. Ongoing trials, especially those evaluating combination of thalidomide with other active cytotoxic agents, will define the role of thalidomide in the therapy of non–plasma-cell malignancies.

Even though the current prescribing system is designed to prevent any possible fetal exposure with this agent, the risk of such an event and the potential for the congenital deformities exist. There are research efforts underway to identify or develop thalidomide analogs with improved antitumor activity with out the teratogenic side effects. One such analog, CC-5013, has already shown promise in myeloma and myelodysplastic syndrome and is being tested in several clinical trials.

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ERRATUM

The June 15, 2004, review article by Kumar et al contained an error in the title.

The correct title is "Thalidomide: Current Role in the Treatment of Non-Plasma Cell Malignancies" (J Clin Oncol 22:2477-2488, 2004).

The online version of the title was corrected in departure from the print.

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